Remarks

Claims 20, 22-33, and 35-44 are currently pending. Claims 32-33 and 37-39 are withdrawn. Claims 20, 22-31, 35-36, and 40-44 stand rejected. Claims 20, 43, and 44 are currently amended to clarify claim language and to specify that the pain is neuropathic pain. These amendments are supported in the specification as originally filed, *inter alia*, on page 13 (lines 11-14) (which indicates that $IB4^+$ neurons are thought to be important in neuropathic pain) and page 9 (lines 9-10) (which indicates that $IB4^+$ neurons express receptors for the GDNF family of neurotrophins). No new matter is introduced by these amendments.

The previous rejection under 35 U.S.C. § 103(a) (levied in the Office Action mailed on December 29, 2008) appears to have been withdrawn.

In the outstanding Office Action mailed September 3, 2009 ("the Office Action"), claims 20, 22-31, 35-36, and 40-44 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner essentially takes the position that the claims are not enabled because (1) allegedly no treatment of pain in humans is provided in the examples and (2) "no information regarding GDNF treatment of pain was known and the best known neurotrophic factor caused pain" in the art at the time of filing.

Even assuming that the Examiner's second point is absolutely true, it would not detract from the enablement of the claimed methods, but rather affirms the novelty and non-obviousness of the present invention. Indeed, no information regarding use of GDNF in the treatment of pain was known in the art at the time of filing because the Applicants were the first to disclose it. That the best known neurotrophic factor at the time (NGF) was known to *cause* pain is a testament to the non-obviousness of the present invention.

Thus, the Examiner's argument with respect to enablement rests on the supposed lack of exemplification of treatment of human patients in the present specification. The Examiner takes

the position that undue experimentation would be required to practice the claimed method. As regards the predictability or unpredictability in the art, the Examiner takes the position that the "claims encompass a large genus of pain, whereas the specification does not teach how to treat all forms of pain." (See the Office Action, page 4.) Without acquiescing to the Examiner's position, and solely in order to advance prosecution, Applicants have amended the claims to refer to a method of treating *neuropathic* pain.

The purpose of the enablement requirement is to ensure that "the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention..." (see MPEP § 2164). As held by the Federal Circuit, "[a]ny part of the specification can support an enabling disclosure, even a background section that discusses, or even disparages, the subject matter disclosed therein" (*Callicrate v. Wadsworth Mfg., Inc*., 427 F.3d 1361, 77 USPQ2d 1041 (Fed. Cir. 2005)). Thus, enabling support is not limited to the exemplification section of a specification.

Furthermore, what is known in the art can be used to support an enabling disclosure: "the scope of enablement… is that which is disclosed in the specification *plus the scope of what would be known to one or ordinary skill in the art* without undue experimentation" (*National Recovery Technologies, Inc. v. Magnetic Separation Systems,* Inc., 166 F.3d 1190, 49 USPQ2d 1671 (Fed. Cir. 1999), emphases added).

The present specification claims priority to, and incorporates by reference the entire contents of, U.S. Application Serial No. 09/354,147 (now issued as U.S. Pat. No. 6,573,067 (the '067 patent)) and International Application No. PCT/US99/02008 (published as WO 99/38889).

Thus, the teachings of the entire disclosures of the present specification, of the '067 patent, and of WO 99/38889, together with what was known in the art at the time of filing, can be used to support enablement of the claimed invention.

In addition, in evaluating the presence or absence of working examples, "an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed invention'. … A rigorous or an invariable exact

correlation is not required…" (Section III.A.2. of "USPTO Training Materials for Examining Patent Applications With Respect to 35 U.S.C. § 112, First Paragraph - Enablement of Chemical/Biotechnological Applications," referencing the holdings of *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. cer. 1985))

The art of the time of the filing included a "clear relationship between abnormal firing in injured afferents… and the paresthesias and pain that often accompany nerve injury" (*i.e.*, neuropathic pain) (Matzner and Devor (1994)[1] (page 349, bottom of the first pargraph in the second column)). The teachings of the present specification, combined with the teachings of the '067 patent and the knowledge in the art at the time, extend this clear relationship to provide a similar correlation between modulation of tetrodotoxin-resistant (TTX-R) currents through sodium channels of dorsal root ganglion (DRG) neurons and modulation of pain.

For example, the '067 patent teaches that "axonal injury… can produce chronic pain (termed neuropathic pain)," and that "changes in the sodium channel profile appear to contribute to abnormal firing that underlies neuropathic pain that patients suffer following axonal injury." (See the '067 patent, column 2 (lines 55-57) and column 3 (lines 14-17). In particular, such changes include "an attenuation of the slowly inactivating, TTX-R current and simultaneous enhancement of the rapidly inactivating, TTX-S [tetrodotoxin-sensitive] Na^+ currents in identified sensory cutaneous afferent neurons following axotomy" (see, *e.g.*, the '067 patent in column 3, lines 4-8).

The '067 patent also teaches that "[a] variety of classes of drugs… act on Na^+ channels" and that "selective blockade or activation (or other modulation) of specific channel subtypes is expected to be of significant therapeutic value." (See column 3, lines 31-37). In particular, the

[1] Matzner and Devor (1994) "Hyperexcitability at Sites of Nerve Injury Depends on Voltage-Sensitive Na^+ Channels," *Journal of Neuroscience*. **72**(1):349-359; submitted herewith in an Information Disclosure Statement.

'067 patent teaches that "[n]ociceptive neurons of the DRG are the major source of the PNS [peripheral nervous system] TTX-R Na^+ current. Thus, the Na^+ channels producing TTX-R currents provide a relatively specific target for the manipulation of pain-producing neurons." (See column 3, lines 41-44). These teachings of the '067 patent were also supported by exemplification demonstrating that expression of NaN (a sodium channel that expresses TTX-R currents) is altered in a model of neuropathic pain. (See Example 16 of the '067 patent, beginning in column 28.)

Applicants were the first to demonstrate that Glial-Derived Neurotrophic Factor (GDNF) modulates expression of NaN and of SNS/PN3 (another sodium channel expressed in DRG that expresses TTX-R). (See Examples 3 and 5 of the specification as originally filed). Applicants were also the first to demonstrate that administration of GDNF modulates TTX-R currents. In particular, Examples 6 and 7 of the present specification show that GDNF modulates TTX-R currents in cultured DRG neurons following *in vitro* axotomy (which is associated with neuropathic pain *in vivo*). Furthermore, Example 8 of the present specification shows that *in vivo* delivery of GDNF to DRG neurons in an animal model of neuropathic pain partially restored TTX-R currents to normal levels after axotomy.

Given the clear correlation between abnormal electrical activity and neuropathic pain known in the art at the time, the demonstrations in the present specification that administration of GDNF partially normalizes TTX-R currents in *in vitro* and *in vivo* animal models of neuropathic pain constitute working examples that support enablement of a method of treatment of neuropathic pain. Furthermore, the present specification provides details on methods of treating pain, including (among other things) routes of administration, dosages, use with other agents, and pharmaceutical formulations. (See, *e.g.*, on pages 15-17.)

Thus, it would not have required undue experimentation for one of ordinary skill in the art reading the present specification to practice the claimed invention.

For reasons stated above, Applicants respectfully requests that this rejection be withdrawn.

CONCLUSION

Applicant again thanks the Examiner for his careful review of the case. Based on the Remarks presented above, Applicant respectfully submits that Claims 20, 22-31, 35, 36, and 40-44 are now in condition for allowance. A Notice to this effect is respectfully requested.

Respectfully submitted,

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